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FORM PTO 1390
(REV 5-93) US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY DOCKET NUMBER
2002-0487A

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)
[NEW] 10/089883

International Application No.	International Filing Date	Priority Date Claimed
PCT/JP00/06963	October 5, 2000	October 5, 1999

Title of Invention
A HUMAN GENE OVER-EXPRESSING ANIMAL AND TEST METHODS USING THE ANIMAL

Applicant(s) For DO/EO/US
Yoshihiro URADE; Yasushi FUJITANI; Hiroaki KITAYAMA; Naoki HAYASHI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.

3. [X] This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [X] A translation of the International Application into English (35 U.S.C. §371(c)(2)). **ATTACHMENT A**

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19.

9. [X] An **unexecuted** oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)). **ATTACHMENT B**

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **ATTACHMENT C**

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [ ] A FIRST preliminary amendment.

    [ ] A SECOND or SUBSEQUENT preliminary amendment.

14. [X] Other items or information:

    a. Cover Page of Published International Application No. WO 01/24627 - **ATTACHMENT D**

    b. International Search Report - **ATTACHMENT E**

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) [NEW] 10/089883	INTERNATIONAL APPLICATION NO. PCT/JP00/06963	ATTORNEY'S DOCKET NO. 2002-0487A

15. [X] The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		
Neither international preliminary examination fee nor international search fee paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00		
International Search Report has been prepared by the EPO or JPO . . . . . $ 890.00		
International preliminary examination fee not paid to USPTO but international search paid to USPTO . . . . . $ 740.00		
International preliminary examination fee paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) . . . . . $ 690.00		
International preliminary examination fee paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) . . . . . $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate		
Total Claims	8 -20 =	0	X $18.00		
Independent Claims	1 - 3 =	0	X $84.00		
Multiple dependent claim(s) (if applicable)			+ $280.00	$ 280.00	
TOTAL OF ABOVE CALCULATIONS =				$1,170.00	
[ ] Small Entity Status is hereby asserted. Above fees are reduced by 1/2.					
SUBTOTAL =				$1,170.00	
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					
TOTAL NATIONAL FEE =				$1,170.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 per property +					
TOTAL FEES ENCLOSED =				$1,170.00	
				Amount to be refunded	$
				Amount to be charged	$

a. [X] A check in the amount of $ 1,170.00 to cover the above fees is enclosed. A duplicate copy of this form is enclosed.

b. [ ] Please charge my Deposit Account No. 23-0975 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

19. CORRESPONDENCE ADDRESS

000513

PATENT TRADEMARK OFFICE

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[CHECK NO. 49659]

[2002-0487A]

DESCRIPTION

A Human Gene Over-expressing Animal and Test Methods Using the Animal

Technical Field

The invention of this application relates to a human gene over-expressing animal, and to various test methods using the animal. More precisely, the invention of this application relates to a non-human transgenic animal which carries, in its somatic cell chromosome, a gene encoding human PGD synthase (H-PGDS), an enzyme for synthesizing prostaglandin D_2 (PGD_2) that is one causal substance for allergy and sleep induction, and which can produce a large amount of PGD_2 through over expression of the enzyme. The invention also relates to methods of using the animal for testing active ingredients of medicines for preventing and curing allergic diseases, sleep disorders, life habit-caused disorders such as obesity.

Background Art

H-PGDS (Biochem. Biophys. Acta 575:43-51, 1979; J. Biol. Chem. 262:3820-3825, 1987; Cell 90:1085-1095, 1997) is an enzyme having the function of producing an endogenous substance, prostaglandin D_2 (PGD_2: Prostaglandins Leukot. Essent. Fatty Acids, 37:219-234, 1989; FASEB J. 5:2575-2581, 1991; J. Lipid Mediat. Cell Signaling, 14:71-82, 1996) that has various physiological activities, and it is expressed in immunocytes and genital organs (J. Immunol. 143:2982-2989, 1989; J. biol. Chem. 270:3239-3246, 1995). It is known that PGD_2 produced from mast cells by

ATTACHMENT A

the action of H-PGDS is involved in excacerbation of inflammations, and its degraded substance, 15d-PGJ_2 (15-deoxy-Δ12,14-PGJ_2) is a differentiation factor for adipose cell (Cell, 83:803-812 & 813-819, 1995).

H-PGDS is expressed in mast cell and antigen-presenting cell (J. Immunol. 143:2982-2989, 1989; J. Biol. Chem. 270:3239-3246, 1995), and participates in production of PGD_2 in allergic inflammation. It is known that thus produced PGD_2 causes bronchoconstriction and vasodilation and involves in ingravescence of allergies.

Of all endogenous sleep-inducing substances that have been clarified up to the present, PGD_2 has the most potent sleep-inducing activity. It is reported that in human patients suffering from trypanosome-infected African sleeping sickness, the PGD_2 level in the cerebrospinal fluid increases 100 to 1,000-fold with ingravescence of the disease condition (Trans Royal Soc. Trop. Med. Hyg. 84:795-799, 1990). In addition, it is known that in pathologic deep sleep observed in systemic mastocytosis patients, the blood PGD_2 level also increases 150-fold (New Engl. J. Med. 303:1400-1404, 1980), and the important role of PGD_2 in pathologic sleep is suggested.

As mentioned above, it is suggested that PGD_2 and H-PGDS producing PGD_2 closely correlate to various physiological functions of individuals, and may be a potential cause of human diseases. However, no animal model system has as yet been established that enables the study under the controlled condition how the over expression of H-PGDS will act on animal.

The invention of this application has been made in consideration of the above-mentioned situation, and its object is to provide a non-human animal that genetically expresses a large amount of H-PGDS. Another object

of this application is to provide methods of using the animal for testing the effectiveness of preventing or curing substances for various diseases caused by the over expression of H-PGDS in the animal.

Disclosure of The Invention

This application provides inventions of the following (1) to (5):

(1) A human gene over-expressing animal, which is a non-human animal carrying a human hematopoietic prostaglandin D_2 synthase gene in its somatic cell chromosome and expressing a large amount of human prostaglandin D_2 synthase, wherein the animal is one obtained through ontogenesis of a totipotency cell of a non-human animal or offspring of the obtained animal, and the totipotency cell is introduced with said synthase gene.

(2) The human gene over-expressing animal of the invention (1), wherein the non-human animal is a mouse.

(3) A method for testing *in vivo* activity of a candidate for the anti-allergy medicines, which comprises administering the candidate to the human gene over-expressing animal of the invention (1) or (2), and measuring allergic reactions of the animal to thereby evaluate the activity of the candidate.

(4) A method for testing *in vivo* activity of sleep-controlling substances, which comprises administering a candidate for the substances to the human gene over-expressing animal of the invention (1) or (2), and measuring sleep condition of the animal to thereby evaluate the activity of the candidate.

(5) A method for testing *in vivo* activity of a differentiation-controlling substance for mast cell and adipose cell, which comprises administering a candidate for the substance to the human gene over-expressing animal of the invention (1) or (2), and measuring the obesity condition of the animal to thereby evaluate the activity of the candidate.

Brief Description of The Drawings

Fig. 1 is a schematic view showing the construction of the transfer vector used in producing a transgenic mouse of this invention.

Fig. 2 shows the results of H-PGDS Northern blot analysis of mRNA extracted from various organs of three lines of transgenic mice and from those of a wild-type mouse.

Fig. 3 shows the results of H-PGDS Northern blot analysis of mRNA extracted from all organs of a transgenic mouse.

Fig. 4 shows the results of H-PGDS enzyme activity data obtained by using fractionations of proteins extracted from various organs of three lines of transgenic mice and from those of a wild-type mouse.

Fig. 5 shows the data of inflammatory cells counted in the wash of air vesicles of antigen-immunized transgenic mice and wild-type mice after exposure to physiological saline or antigen.

Fig. 6 shows the data of spontaneous locomotor for 12-hours of transgenic and wild-type mice with intraperitoneal administration of

lipopolysaccharide (20 mg/kg).

Fig. 7 shows the data (A) of body weight change of transgenic (TG) and wild-type (WT) mice fed with a high-fat food, and the data (B) of white adipose tissue weight of the mice fed with a normal food or a high-fat food.

The Best Mode for Carrying Out The Invention

For the transgene, human H-PGDS gene, its cDNA can be used. The H-PGDS cDNA may be prepared according to a method that comprises synthesizing an oligonucleotide based on the base sequence of a desired part of a known rat cDNA sequence (Cell 90:1085-1095, 1997; GenBank Accession No. D82071) or human cDNA sequence (Eur. J. Biochem. 267:3315-3322, 2000; GenBank Accession No. NM014485), and using it as a probe to screen a human cDNA library, or an RT-PCR method that comprises synthesizing oligonucleotides capable of hybridizing sequences at both ends of the intended cDNA fragment, and using it as primers to prepare the H-PGDS cDNA from an mRNA isolated from human cells.

The transgene has a promoter sequence or an enhancer sequence linked thereto, which is for controlling the over expression of the gene. The promoter sequence or the enhancer sequence are not specifically defined, for which, for example, suitably used is a promoter region or an enhancer region of a gene capable of being highly expressed in various organs of the transgenic animal.

The human gene over-expressing animal of the invention (1) can be produced in accordance with a known method of producing transgenic animals (for example, Proc. Natl. Acad. Sci. USA 77:7380-7384, 1980).

Specifically, the transgene is introduced into totipotency cell of a non-human animal, the cell is ontogenized into individuals, and those carrying the transgene in the genome of the somatic cells thereof are selected. The thus-selected individuals are of the intended transgenic animal. From the technical viewpoint, animals of any and every species may be employed for the non-human animal for use herein, but mice are the best for it, since a large number of inbred lines have been available and, in addition, the technique of fertilized egg incubation and external fertilization thereof has been established in the art. Of mice, the totipotency cell to be introduced with the gene may be those of fertilized eggs or early embryos. For gene introduction into cultured cell, DNA microinjection method is the best in view of the yield of the transgenic animals and of the transgene transfer efficiency to the next generations.

The fertilized eggs into which the gene has been injected are implanted into the oviduct of a surrogate mother, in which the eggs are ontogenized into an individuals, and the individual animals are born from it and then are bred by a foster mother. Thus bred, DNA is extracted out of the animal at a part of its body (the tip of the tail), and subjected to Southern blotting analysis or PCR to confirm the presence of the transgene. The individual animal in which the presence of the transgene has been confirmed is the founder, and the transgene is transferred to 50 % of the offspring of the founder. In that manner, wild-type or variant animals can be produced efficiently.

The thus-produced transgenic animal produces excess H-PGDS, and therefore can be the best model for investigating the physiological activities of PGD_2.

The invention (3) of this application is a method for testing *in vivo*

activity of a candidate for anti-allergy medicines, which comprises administering the candidate to the human gene over-expressing animal of the invention (1), and measuring the allergic reaction in the animal to thereby evaluate the activity of the candidate. Specifically, the transgenic animal of the invention (1) carries a large amount of H-PGDS and produces a large amount of PGD_2, and therefore sensitively reacts with various types of allergens. Accordingly, for example, when a certain allergen is previously administered to the animal, a candidate for anti-allergy medicine is then thereto, and the systemic allergic reaction of the animal is measured, then the pharmacological activity of the candidate can be evaluated.

The invention (4) of this application is a method for testing *in vivo* activity of a sleep-controlling substance, which comprises administering a candidate for the substance to the human gene over-expressing animal of the invention (1), and measuring the sleep condition of the animal to thereby evaluate the activity of the candidate. Specifically, the transgenic animal of the invention (1) carries a large amount of H-PGDS and produces a large amount of PGD_2, and therefore its sleep control is disordered due to the strong sleep-inducing action of PGD_2. Accordingly, for example, when a candidate for sleep control (for example, a substance having the ability to sustain vigilance) is administered to the animal and the awake/sleep condition of the animal is measured, and then the pharmacological activity of the candidate can be evaluated. The awake/sleep condition of the animal can be determined by measuring the locomotor activity thereof or measuring the food intake or water intake thereof, or by measuring the physiological parameters such as electroencepharogram or electromyogram thereof.

The invention (5) of this application is a method for testing *in vivo* activity of a candidate for anti-obesity medicine, which comprises administering a candidate for anti-obesity medicine to the human gene

over-expressing animal of above (1), and measuring the degree of obesity of the animal (e.g., body weight, fatty tissue weight) to thereby evaluate the activity of the candidate. Specifically, the transgenic animal of the invention (1) carries a large amount of H-PGDS and produces a large amount of PGD_2, and therefore produces a large amount of 15d-PGJ_2 that involves in increase of the body weight or fatty tissue weight in the animal, and, as a result, the animal gets fat. Accordingly, for example, when a candidate for anti-obesity is administered to the animal and the degree of the obesity of the animal is measured, and then the pharmacological activity of the candidate can be evaluated.

Examples

The invention of this application is described in more detail and concretely with reference to the following Examples, which, however, are not intended to restrict the scope of the invention of this application.

Example 1

(1) Production of Transgenic Mice:

From the cDNA library prepared from mRNA of human cells, human H-PGDS cDNA was cloned by using rat H-PGDS cDNA as a probe.

Next, the human H-PGDS cDNA was inserted and linked into a cloning site (SalI/NotI) of the vector (pCAGGS) to construct a transfer vector. Fig. 1 shows the construction of the transgene in the transfer vector. As in Fig. 1, the transgene has a CMV enhancer and a chicken β-actin promoter upstream the H-PGDS cDNA, and when introduced into a mouse chromosome, it expresses a large amount of H-PGDS mRNA owing to the

action of the enhancer and the promoter.

The transfer vector was introduced into fertilized eggs of an FVB mouse through microinjection. The gene-introduced fertilized eggs were then implanted into the oviduct of a surrogate mother in an ordinary manner, in which those are ontogenized into individuals, and the individuals were then born.

DNA was extracted from the tail of each of the thus-obtained mouse individuals, and it was analyzed through Southern blotting analysis using a probe that had been synthesized on the basis of the sequence of the transgene. Based on the data of the thus-analyzed DNA, transgenic mice were selected. Three independent lines of transgenic mice were thus established, which differ from each other in the degree of H-PGDS expression therein. The data are as in Fig. 2.

(2) Investigation of Gene Expression in Transgenic Mice:

Systemic expressions of the transgene of the transgenic mice were examined with Northern blot analysis. As a result, it was confirmed that in S55 mouse, the H-PGDS gene was expressed to a high level in the skeletal muscle, the heart, the lung, the large intestine and the liver. The data are as in Fig. 3.

(3) Investigation of PGD Enzyme Activity in Transgenic Mice:

Using a substrate PGH_2, the PGD enzyme activity in various organs of the transgenic mice was determined. In the transgenic mice, the enzyme activity significantly increased in various organs. The three lines of transgenic mice were compared with each other in point of the enzyme activity thereof. The enzyme activity increase in these was in an order of S55 > S41 > S66. The data are as in Fig. 4.

Example 2

As a human asthma model, the transgenic mice obtained in Example 1 were analyzed in antigen-induced lung inflammation model.

After antigen challenge, the invasion of eosinophilic leukocytes into the lung of the transgenic mice significantly increased, as compared with that into the lung of the wild-type mice. The data are as in Fig. 5.

The result as above confirms that the transgenic mice of this invention are useful as a model animal for clarifying the mechanism of allergosis and are effective for the system of screening novel anti-allergy substances.

Example 3

A lipopolysaccharide was intraperitoneally administered to the transgenic mice obtained in Example 1, and the inflamed mice in narcolepsy were analyzed.

Concretely, a high-concentration (20 mg/kg) lipopolysaccharide was administered to the transgenic mice, and the spontaneous locomotor of each mouse was observed. As a result, the spontaneous locomotor of the transgenic mice significantly lowered as compared with that of the wild-type mice. This suggests that the sleep time of the transgenic mice increased. The data are as in Fig. 6.

The result as above confirms that the transgenic mice of this invention are useful as a model animal for clarifying the mechanism of sleep induction and are effective for the system of screening novel substances of controlling sleep-awake rhythm.

Example 4

The transgenic mice obtained in Example 1 and wild-type mice were loaded with a high-fat food, and analyzed for the obesity progress.

Concretely, the mice were loaded with a high-fat food for 6 weeks, and their body weight increase was observed. As compared with that of the wild-type mice, the body weight of the transgenic mice significantly increased. In addition, the white adipose tissue weight of the transgenic mice also significantly increased. The data are as in Fig. 7.

Industrial Applicability

As described in detail hereinabove, the invention provides a transgenic animal that expresses a large amount of H-PGDS and therefore produces a large amount of PGD_2. The animal promotes the development of medicines for various human diseases.

CLAIMS

1. A human gene over-expressing animal, which is a non-human animal carrying a human hematopoietic prostaglandin D_2 synthase gene in its somatic cell chromosome and expressing a large amount of human prostaglandin D_2 synthase, wherein the animal is one obtained through ontogenesis of a totipotency cell of a non-human animal or offspring of the obtained animal, and the totipotency cell is introduced with said synthase gene.

2. The human gene over-expressing animal of claim 1, wherein the non-human animal is a mouse.

3. A method for testing *in vivo* activity of a candidate for the anti-allergy medicines, which comprises administering the candidate to the human gene over-expressing animal of claim 1 or 2, and measuring allergic reactions of the animal to thereby evaluate the activity of the candidate.

4. A method for testing *in vivo* activity of sleep-controlling substances, which comprises administering a candidate for the substances to the human gene over-expressing animal of claim 1 or 2, and measuring sleep condition of the animal to thereby evaluate the activity of the candidate.

5. A method for testing *in vivo* activity of a differentiation-controlling substance for mast cell and adipose cell, which comprises administering a candidate for the substance to the human gene over-expressing animal of claim 1 or 2, and measuring the obesity condition of the animal to thereby evaluate the activity of the candidate.

ABSTRACT

The present application provides a human gene over-expressing animal, which is a non-human animal carrying a human hematopoietic prostaglandin D_2 synthase gene in its somatic cell chromosome and expressing a large amount of human prostaglandin D_2 synthase, wherein the animal is one obtained through ontogenesis of a totipotency cell of a non-human animal or offspring of the obtained animal, and the totipotency cell is introduced with said synthase gene. The present application also provides a method of using the transgenic animal for testing *in vivo* activity of a candidate for anti-allergy medicines, sleep-controlling substances and candidates for anti-obesity.

Fig. 1

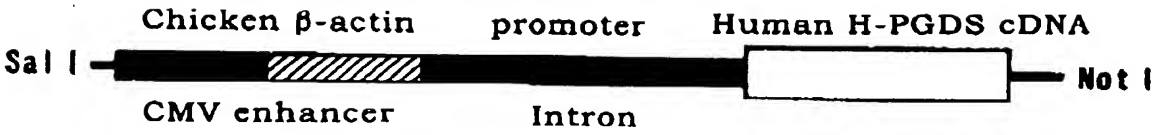

Chicken β-actin
promoter
Human H-PGDS cDNA
Sal I
Not I
CMV enhancer
Intron

Fig. 2

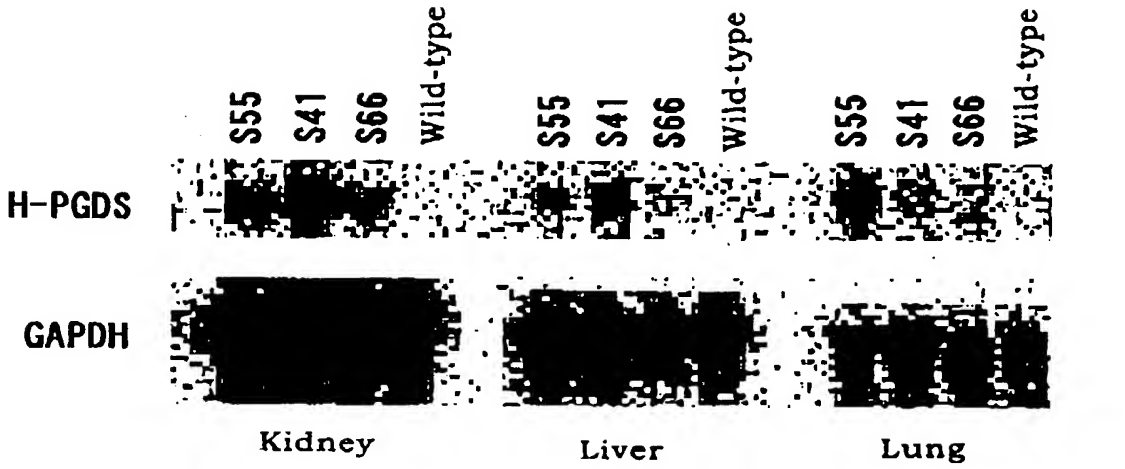

S55
S41
S66
Wild-type
S55
S41
S66
Wild-type
S55
S41
S66
Wild-type
H-PGDS
GAPDH
Kidney
Liver
Lung
10μg total RNA/lane

Fig. 3

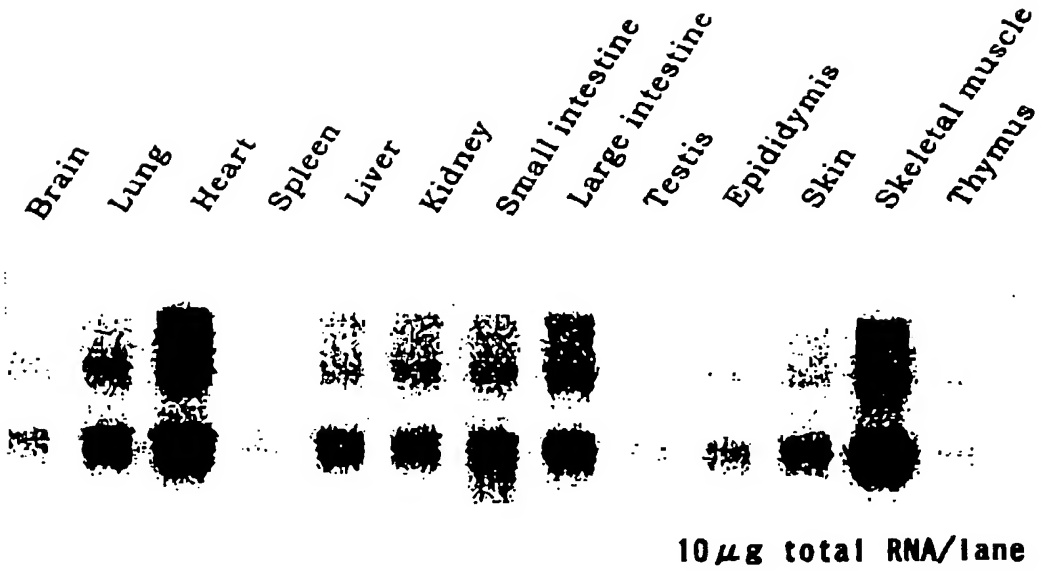

Brain
Lung
Heart
Spleen
Liver
Kidney
Small intestine
Large intestine
Testis
Epididymis
Skin
Skeletal muscle
Thymus
10μg total RNA/lane

Fig. 4

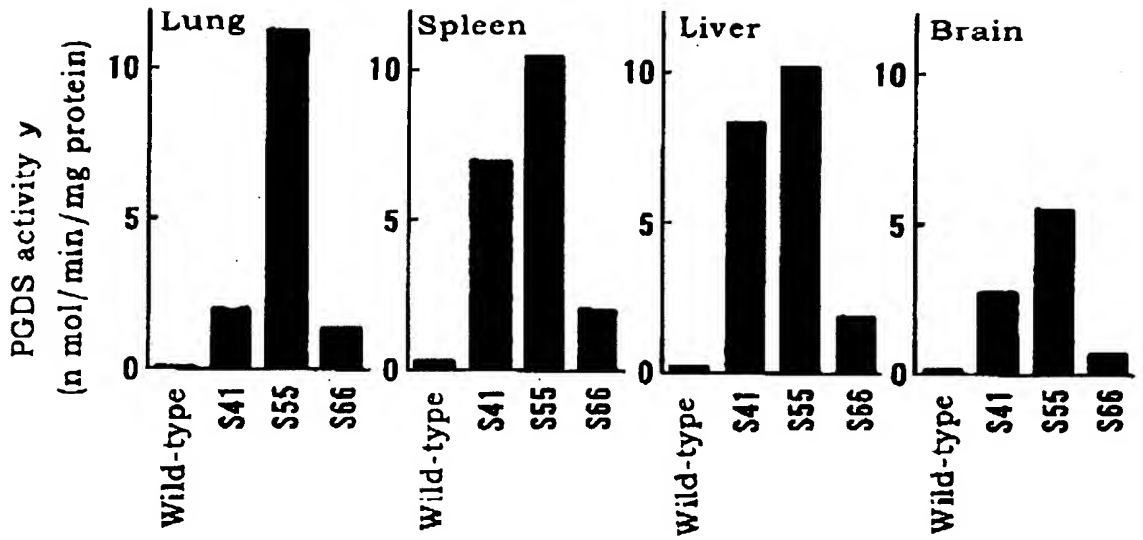

PGDS activity y
(n mol/min/mg protein)
Lung
Spleen
Liver
Brain
10
5
0
Wild-type
S41
S55
S66

Fig. 5

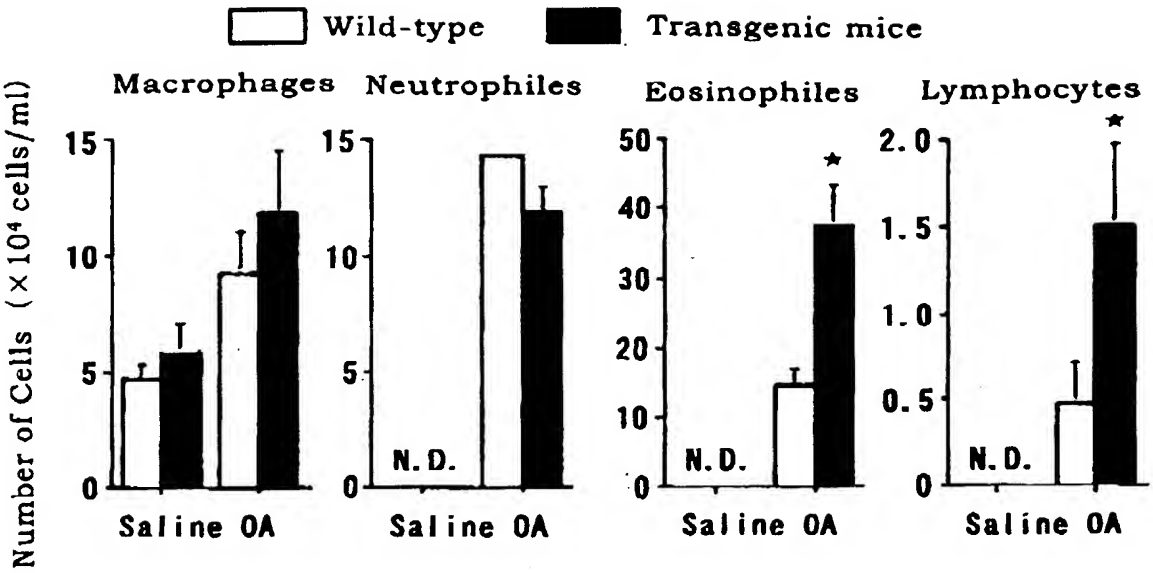

Wild-type
Transgenic mice
Macrophages
Neutrophiles
Eosinophiles
Lymphocytes
Number of Cells (×10⁴ cells/ml)
15
10
5
0
50
40
30
20
2.0
1.5
1.0
0.5
N.D.
Saline
OA
★

Fig. 6

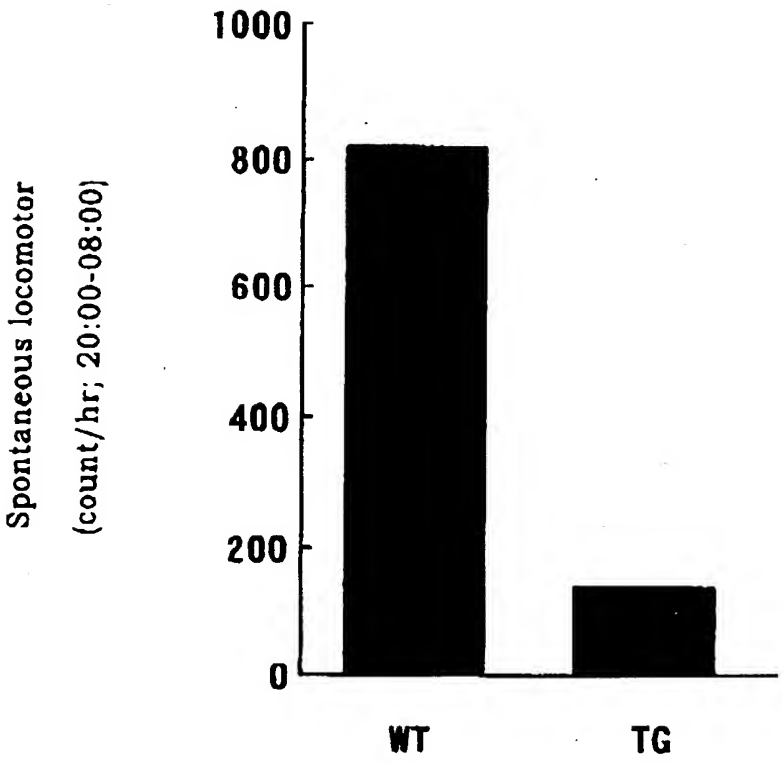
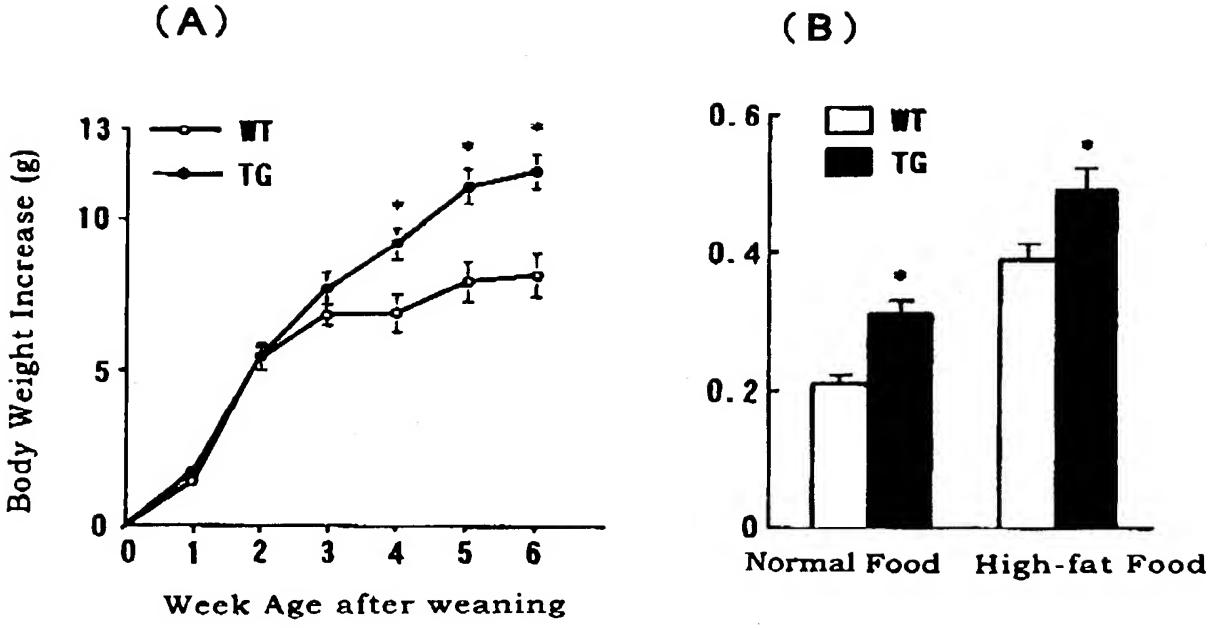

Spontaneous locomotor
(count/hr; 20:00-08:00)
1000
800
600
400
200
0
WT
TG

Fig. 7


(A)
(B)
WT
TG
Body Weight Increase (g)
13
10
5
0
0 1 2 3 4 5 6
Week Age after weaning
0.6
0.4
0.2
0
Normal Food
High-fat Food

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

( ) Original ( ) Supplemental ( ) Substitute (X) PCT ( ) DESIGN

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: A HUMAN GENE OVER-EXPRESSING ANIMAL AND TEST METHODS USING THE ANIMAL

of which is described and claimed in:
( ) the attached specification, or
( ) the specification in application Serial No. ________________, filed __________________, and with amendments through ________________, or
(X) the specification in International Application No. PCT/JP00/06963, filed October 5, 2000 , and as amended on ___________________ (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	1999-284610	October 5, 1999	Yes
Japan	2000-166726	June 2, 2000	Yes

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys and agents named herein to accept and follow instructions from NISHIZAWA & ASSOCIATES as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date April 5, 2002

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Title of Invention A HUMAN GENE OVER-EXPRESSING ANIMAL AND TEST METHODS USING THE ANIMAL